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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/613,222	07/03/2003	Joseph Rubinfeld	12636.330.301	7039

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EXAMINER	
NICKOL, GARY B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 04/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/613,222	RUBINFELD ET AL.	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *59-76* is/are pending in the application.

4a) Of the above claim(s) *70-72* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *59-69 and 73-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Re: Rubinfeld *et al.*

Date of priority: 02-21-2001

DETAILED ACTION

Election/Restrictions

The applicants note (Response, 01-20-2006, page 5) that due to an oversight by the Examiner, the Restriction Requirement mailed 11-21-2005 did not include the Preliminary Amendment filed October 27, 2003. However, to expedite this matter, pursuant to 37 C.F.R. 1.142, Applicants elect Group II, without traverse.

The preliminary amendment filed 10-27-2003 indicated that claims 1-58 were cancelled. New claims 59-76 were presented which are consistent with applicant's elected Group II. However, it is noted that the previous restriction requirement also required an **election of species** (see pages 3-4 of Restriction mailed 11-21-2005) to the type of benign and malignant tumors claimed and to various species of alkylating agents, all of which were presented in the preliminary amendment. Thus, though the requirement for a restriction between the two groups is vacated, the requirement for a species election is maintained.

During a telephone conversation with Maya Skubatch on April 6, 2006 a provisional election was made to the species of **platinum compounds (Claim 69), hemangiomas (Claim 74), and ovarian tumor (Claim 76).** *Affirmation of this election must be made by applicant in replying to this Office action.* Applicant is reminded that

upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

To summarize:

Claims 59-76 are pending.

Claims 70-72, drawn to non-elected species, are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claims 59-69, and 73-76 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 64 recites the limitation "2-50 mg/m^2" in Claim 59. There is insufficient antecedent basis for this limitation in the claim. Claim 59 specifically recites that the DNA methylation inhibitor is administered at a dose **below** 50 mg/m^2. Thus, the upper limit of the administered dose cannot be 50 mg/m^2 as claimed in Claim 64.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 59-62, 64-65, 67-69, 75-76 are rejected under 35 U.S.C. 102(b) as being anticipated by Lenzi *et al.* (International Jnl. Oncology, 1995, Vol. 6 (2), pages 447-450).

Lenzi *et al.* teach a method for treating a patient having a tumor comprising administering to the patient a DNA methylation inhibitor, 2'-deoxy-5-azacytidine (a cytosine analog), in combination with a therapeutically effective amount of an anti-neoplastic agent (cisplatin- a **platinum** compound) wherein the disease associated with abnormal cell proliferation is a malignant tumor including colorectal, head and neck, non-small cell lung, breast, and pancreatic tumors (page 449, 2nd column). The specification teaches (page 17, line 1) that decitabine is equivalent to 5-aza-2'-deoxycytidine. Thus, for examination purposes it was assumed that the prior art *2'-deoxy-5-azacytidine* was equivalent to 5-aza-2'-deoxycytidine.

Lenzi *et al.* further teach that decitabine is administered intravenously to the patient per day at a dose below 50 mg/m^2 . The dosages of decitabine included 10, 20, 30, 40 and 50mg/ m^2 (Table II, page 449). The reference further teaches that decitabine was administered intravenously over 30 minutes each day for 3 consecutive days followed by the administration of cisplatin on day 4. Thus, the DNA methylation inhibitor was administered prior to the alkylating agent. Additionally, although the reference does not specifically teach that the activity of the administered alkylating agent is "adversely

affected by aberrant DNA methylation" (Claim 67), applicant's disclosure clearly includes cisplatin as one of the many anti-neoplastic agents whose activity in vivo is adversely affected by aberrant DNA methylation (page 7, line 24; page 20 lines 5-22).

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 59-64, 67-69, 75-76 are rejected under 35 U.S.C. 102(a) as being anticipated by Plumb *et al.* (Cancer Research, Vol.60, pages 6039-6044, November 1, 2000).

Plumb *et al.* teach a method for treating a patient having a tumor comprising administering to the patient having the disease a therapeutically effective amount of a DNA methylation inhibitor , 2'-deoxy-5-azacytidine, in combination with a therapeutically effective amount of an anti-neoplastic agent (cisplatin) wherein the disease associated with abnormal cell proliferation is cancer including ovarian and colon cancer (see page 6041, 1st and 2nd columns under "Effect of DAC on Drug Sensitivity"; also see Figure 4). The specification teaches (page 17, line 1) that decitabine is equivalent to 5-aza-2'-deoxycytidine. Thus, for examination purposes it is assumed that 2'-deoxy-5-azacytidine is equivalent to 5-aza-2'-deoxycytidine.

The reference further teaches (1st column, top of page 6040) that the total dosage per day was 15 mg/kg. This is approximately equivalent to 45.24 mg/m^2 (see attached dose calculator; taken from, http://www.fda.gov/cder/cancer/animalframe.htm).

Further, according to the online version of the Stedman's Medical Dictionary, subcutaneous is defined as "beneath the skin". Since the specification does not

specifically define "subcutaneously", it is assumed for examination purposes that any type of administration occurring beneath the skin is a subcutaneous administration.

Thus, Plumb *et al.* further teach that the DNA methylation inhibitor (decitabine) is administered intraperitonealy (ip) (Figure 4) (Claims 28-30). Since an intraperitional injection occurs beneath the skin, the claims read on a subcutaneous administration and or an administration beneath the skin. Plumb *et al.* further teach that the DNA methylation inhibitor is administered prior to the administration of the anti-neoplastic agent (page 6043, 1st column, 1st line).

Additionally, although the reference does not literally teach that the activity of the anti-neoplastic agent (cisplatin) in vivo is "adversely affected by aberrant DNA methylation", Applicant's disclosure clearly includes cisplatin as one of the many anti-neoplastic agents whose activity in vivo is adversely affected by aberrant DNA methylation (page 7, line 24; page 20 lines 5-22).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the

various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 59-64, 66, and 73-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/01118 (Atherogenics, Inc., January 1999, **IDS**) in further view of Lenzi *et al.* (International Jnl. Oncology, 1995, Vol. 6 (2), pages 447-450).

WO 99/01118 teaches (page 83, line 5) a method for treating a patient having a tumor comprising administering to the patient a DNA methylation inhibitor (decitabine) wherein the inhibitor is administered intravenously or subcutaneously or in a slow release dosage form (page 48) wherein the tumor is a benign tumor such as a hemangioma (page 46 and 84) or a cancer of the ovaries (page 47 and 85).

WO 99/0118 does not specifically teach that the dosage of the DNA methylation inhibitor (decitabine) is at a dose below 50 mg/m^2 (Claim 59), or a dose ranging from 2-50 mg/m^2 (Claim 64).

Through phase I and II trials of a laboratory-derived synergistic combination of cisplatin and 2'-deoxy-5-azacytidine (decitabine) in cancer patients, Lenzi *et al.* teach that the

maximum tolerated dose of decitabine is 50 mg/m^2, absent any patient toxicity. However, Lenzi *et al.* caution that the dosage should be lowered in certain patients that accrue various side effects such as granulocytopenia with infection and thrombocytopenia associated with bleeding or grade 4 nonhematological toxic effects. In such cases, the dosage of decitabine was reduced to 30 mg/m^2 (see page 448, 1st column, last paragraph). Further, the reference teaches that dose modification to 40 mg/m^2 was necessary upon hematological toxicity with an AGC of <500 cells/mm^3 or a platelet count of <50,000 cells/mm^3 or if nonhematological toxic effects grade 3 were seen.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to include the administration of decitabine at a dosage below 50 mg/m^2 and or ranging between 2 and 50mg/m^2. One would have been motivated to do so because Lenzi *et al.* suggest that the maximum tolerated dose (MTD) of decitabine is 50 mg/m^2 absent patient toxicity. However, those of ordinary skill in the art immediately recognize that patient toxicity is often a limiting factor in dose responses and that for some patients the MTD will invoke serious side effects. For example, Lenzi *et al.* caution that the dosage should be lowered in certain patients that accrue various side effects such as granulocytopenia with infection and thrombocytopenia associated with bleeding or grade 4 nonhematological toxic effects. In such cases, the dosage of decitabine was reduced to 30 mg/m^2 (see page 448, 1st column, last paragraph). Further, Lenzi *et al.* teach that dose modification to 40 mg/m^2 was necessary upon hematological toxicity with an AGC of <500 cells/mm^3 or a platelet count of <50,000 cells/mm^3 or if nonhematological toxic effects grade 3 were seen. Thus, because one of ordinary skill in

the art would not reasonably expect that all patients being treated would safely tolerate decibitane at 50 mg/m^2, one of ordinary skill would successfully reason that a subset of patients must be administered *less* than the MTD of decitabine.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 59-65, 67-69, and 75-76 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5, 7-11 of U.S. Patent No. 6,613,753. Although the conflicting claims are not identical, they are not patentably distinct from each other because the current application is broadly drawn to a method of treating a patient having a tumor comprising administering (intravenously or subcutaneously) to the patient a DNA methylation inhibitor at a dose below 50 mg/m^2

wherein the DNA methylation inhibitor is decitabine further comprising administering an alkylating agent which is a platinum compound (whose activity is adversely affected by aberrant DNA methylation). These claims clearly overlap or render obvious the patented claims of treating cancer comprising administering decitabine from 1-20mg/m^2 per day in combination with an antineoplastic agent whose activity in vivo is adversely affected by aberrant DNA methylation wherein the anti-neoplastic agent is cisplatin or carboplatin (i.e., platinum compounds). "A generic claim cannot be allowed to an applicant if the prior art discloses a species falling within the claimed genus." The species in that case will anticipate the genus. In re Slayter, 276 F.2d 408, 411, 125 USPQ 345, 347 (CCPA 1960); In re Gosteli, 872 F.2d 1008, 10 USPQ2d 1614 (Fed. Cir. 1989).

Provisional Double Patenting:

Claims 59-65, 67-69, and 73-76 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7, 14-17, and 19 of copending Application No. 10/867621. Although the conflicting claims are not identical, they are not patentably distinct from each other because the current application is broadly drawn to a method of treating a patient having a tumor comprising administering (intravenously or subcutaneously) to the patient a DNA methylation inhibitor at a dose below 50 mg/m^2 wherein the DNA methylation inhibitor is decitabine further comprising administering an alkylating agent which is a platinum compound. These claims are represent an obvious variation from the pending claims drawn to a method of inhibiting a disease associated with abnormal cellular proliferation comprising administering to a patient a DNA methylation inhibitor at a dose of 1-100mg/m^2 in

combination with a therapeutically effective amount of a platinum compound. Both sets of claims treat the same conditions with the same compounds within the same dosage requirements. Thus, although the claims are not identical, there is no patentable distinction between the two pending claim sets.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 571-272-0835. The examiner can normally be reached on M-Th, 8:30-5:30; alternate Fri., 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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